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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/558,149	04/26/2000	Nicholas Nicolaides	01107.00004	1171

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Banner & Witcoff Ltd
1001 G Street N W
Washington, DC 20001-4597

EXAMINER

SHUKLA, RAM R

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 01/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/558,149

Applicant(s)

NICOLAIDES ET AL.

Examiner

Ram R. Shukla

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 November 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 14, 19, 20, 29, 53, 58-62 and 69-80 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 14, 19, 20, 29, 53, 58-62 and 69-80 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 26 April 2000 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on **11-05-2003** has been entered.
2. New claims 69-80 have been entered.
3. Claims 14, 19, 20, 29, 53, 58-62, 69-80 are pending and under consideration.
4. It is noted that this application is a divisional of US 09/059,461 filed 4-14-1998. While the first sentence of the specification provides reference to the parent application as allowed, it does not list the US patent number. Applicants are required to include the patent number in the first sentence to comply with the 25 US 120.
5. The declaration under 37 CFR 1.131 by Nicholas Nicolaides has been considered.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 14, 19, 20, 29, 53, 58-62, 69-80 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: (i) a transgenic mouse in whose all germ and somatic cells a polynucleotide encoding a dominant negative allele of a PMS2 mismatch repair gene disclosed in SEQ ID NO 1 is

integrated, wherein said dominant negative allele comprises a truncation mutation and wherein said dominant negative allele of said PMS2 causes a mismatch repair defect in the cells of the transgenic mouse, and wherein cells and tissues of said transgenic mouse have defect in mismatch repair; (ii) a method of making said transgenic mouse, wherein said method comprises introducing into a mouse fertilized egg a polynucleotide comprising a nucleic acid sequence encoding a dominant negative allele of PMS2 mismatch repair gene disclosed in SEQ ID NO 1, wherein said dominant negative allele of said PMS2 causes a mismatch repair defect, implanting the fertilized egg comprising the polynucleotide into a pseudopregnant female mouse, whereby the fertilized egg develops into a mature mouse and wherein cells and tissues of said transgenic mouse have defect in mismatch repair, does not reasonably provide enablement for other embodiments of the claimed invention for reasons of record set forth in the previous office actions of 7-5-01, 3-26-02, 12-28-02, 6-16-2003. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Response to Arguments

Applicant's arguments filed 11-15-03 have been fully considered but they are not persuasive to obviate all the grounds of rejection.

It is noted that while applicants limited their invention to mainly a transgenic mouse, method of making a transgenic mouse and method of using the transgenic mouse, amendments to claims and the newly presented claims present issues of enablement as discussed below.

First, applicants amended claim 62 by adding the limitation "murine" which includes both mouse and rat and as discussed in the previous office actions, method of making a transgenic rat is not enabled. Next, the claims as instantly recited encompass any PMS2 mismatch repair gene and as discussed in the previous office actions, this aspect is not enabled. Applicants have argued that truncations in PMS2 proteins of several organisms were known and that Arabidopsis

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thaliama PMS2 protein was known to render bacteria hypermutable and applicants provide a declaration by Nicholas Nicolaides, such does not provide enabling support for the full scope of the claimed invention because the claimed invention does not just include a truncated PMS2 protein but it includes method of making a transgenic mouse with different constructs and getting transgenic mouse of the same phenotype. As discussed in the previous office actions, while one could produce a transgenic mouse with different constructs, it would be unpredictable as to what would be the phenotype of the resultant transgenic mouse. It is noted that while Arabidopsis PMS2 works in bacteria, there is no evidence that a bacterial or Arabidopsis PMS2 will work in mouse cells and even if worked in vitro in mouse cells, it would be unpredictable whether a transgenic mouse made by integrating bacterial or Arabidopsis PMS2 truncation mutants will have the mismatch repair defect as observed with human PMS2 truncation mutant. It is emphasized that all the organisms do not comprise PMS2, rather they have PMS2 homologs, which have varying degree of sequence homology and difference among different proteins of different species.

Claim 60 recites a transgenic mouse whose 50% cells comprise the transgene, however, neither the art of record nor the specification teaches how to make such a transgenic mouse. At the time of the invention, while it was routine to make a transgenic mouse whose all somatic and germ cells comprised a transgenic, neither the art of record nor the specification provided any guidance how to make a transgenic mouse whose at least 50% somatic and germ cells comprising a transgene, in view of the unpredictability issues related to transgenesis as discussed in the previous office action. For example, if only 50% of the mouse comprised the gene, how would an artisan know how to use such a mouse in whose tissues only half of the cells would comprise a transgene.

Claim 61 and 76 recites a transgenic mouse produced by a process comprising introducing a polynucleotide in a mouse. Again, the specification does not teach how to make a transgenic mouse by introducing a polypeptide in a mouse and it was known in the art to make a transgenic mouse by this method. If there is such a method, applicants have not provided any evidence in this regard.

Newly presented claim 71, recites a method for generating a mutation in a gene of interest by growing a mouse comprising a gene of interest and a polynucleotide encoding a dominant negative allele of a PMS2 mismatch repair gene, however, the specification does not teach how to make and use such a mouse and grow such a mouse. It is noted that the specification (in view of the declaration by Dr. Bradford Kline) only supports the making and using of a transgenic mouse whose all germ and somatic cells a polynucleotide encoding a dominant negative allele of a PMS2 mismatch repair gene disclosed in SEQ ID NO 1 is integrated, wherein said dominant negative allele comprises a truncation mutation and wherein said dominant negative allele of said PMS2 causes a mismatch repair defect in the cells of the transgenic mouse, and wherein cells and tissues of said transgenic mouse have defect in mismatch repair.

Double Patenting

8. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

9. Claims 29, 52, 53 and 58-61 remain provisionally rejected and claims 63-68 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 13-18 and 45-50 of co-pending Application No. 09/853,645 for reasons of record set forth in the previous office action of 12-28-02. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Applicants' reiteration of the request for abeyance of this rejection until indication of allowable claims is noted.

10. No claim is allowed.

11. Allowable subject matter:

- (i) A transgenic mouse in whose all germ and somatic cells a polynucleotide encoding a dominant negative allele of a PMS2 mismatch repair gene disclosed in SEQ ID NO 1 is integrated, wherein said dominant negative allele comprises a truncation mutation and wherein said dominant negative allele of said PMS2 causes a mismatch repair defect in the cells of the transgenic mouse, and wherein cells and tissues of said transgenic mouse have defect in mismatch repair;
- (ii) a method of making said transgenic mouse, wherein said method comprises introducing into a mouse fertilized egg a polynucleotide comprising a nucleic acid sequence encoding a dominant negative allele of PMS2 mismatch repair gene disclosed in SEQ ID NO 1, wherein said dominant negative allele of said PMS2 causes a mismatch repair defect, implanting the fertilized egg comprising the polynucleotide into a pseudopregnant female mouse, whereby the fertilized egg develops into a mature mouse and wherein cells and tissues of said transgenic mouse have defect in mismatch repair; and
- (iii) a method of using said transgenic mouse as recited in claims 72-75.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for TC 1600 is (703) 703-872-9306. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the William Phillips whose telephone number is (703) 305-3413.

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Please note that effective January 13, the offices for Examiner Shukla, SPE Reynolds and LIE William Phillips will move to the new USPTO location in Alexandria, VA and their phone numbers will change. The new phone numbers will be as follows:

Ram Shukla: **(571) 272-0735**

Deborah Reynolds: **(571) 272-0734**

William Phillips: **(571) 272-0548**

Ram R. Shukla, Ph.D.
Primary Examiner
Art Unit 1632



RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER